cause of lung cancer associated with inhalation of industrial pollutants.

Animal Experiments of Industrial Pollutants that are also Cigarette Smoke Constituents

The last section on occupational/environmental factors is concerned with studies relating to industrial chemicals that coincidentally are present in cigarette smoke and 'tobacco tar.' Although their presence in tobacco smoke and industrial emissions has been recognized during the 1940's, differences in concentration have been overlooked. The political situation in Europe and the United States during the 1940's had influenced the credibility of German scientists, including the Nazi doctors, who conducted toxicologic research in human prisoners. After World War II, it became apparent that intravenous phenol was used for selective euthanasia. During the early years of Nazism, some German scientists published that phenol was a naturally occurring substance in the human body. Also during the late 1930's, German scientists wrote the first complete monograph on toxicity of industrial chemicals that was translated into English by authority of the Alien Property Custodian (4304). It is not known how much of these chemicals were tested in concentration camps and only phenol has been identified. The materials relating to Nazism in medicine are being submitted in the form of two monographs (8601) (8602), and an article on occupational

cancer among Jewish and non-Jewish population of the Netherlands (4978).

Benzpyrene in tobacco tar. Hieger, from Research Institute of the Royal Cancer Hospital, London, was credited as the first scientist who characterized the fluorescence spectrum of 3:4-benzpyrene (3739). He used visual examination of photographs of fluorescence spectra, and patiently separated, isolated and identified 3:4-benzpyrene from coal tar pitch. The synthetic solution of benzpyrene was used to identify and separate it from contaminants in coal pitch. Tobacco tar tested by Hirst did not contain the fluorescence bands characteristic of benzpyrene (3230). Roffo & Roffo Jr. reported isolating benzpyrene in 1939 and 1940 (3942) (4017). Roffo used destructive distillation whereas Hirst collected tobacco tar at a lower temperature. Also in 1940, Roffo proposed legislation on prevention of cancer associated with industrialization (4019). This article needs to be added to Spanish publications needing English translation.

Benzpyrene was not tested by inhalation in experimental animals because a chamber designed to administer the substance in an appropriate solvent was not yet available. Carlson and Adams, from the University of Chicago, surgically produced persistent bronchial fistulating rats and rabbits specifically for the purpose of direct application of suspected carcinogens to the bronchial mucosa. I have selected their report as a highlight publication (4326). Three months of applications, every other

day, did not induce any definite "gross evidence of cancer." I have not found a followup article on microscopic examination of tissues and detailed results of studies that were in progress.

Oxides in tobacco smoke and fuel combustion. Carbon monoxide was the most widely investigated constituent of tobacco smoke and fuel combustion (2701) (3339) (4206) (4261). Carbon monoxide had not been suspected as a carcinogen. However, animals exposed to low levels of carbon monoxide were less sensitive to tar skin cancer in mice (3636). The influence of carbon monoxide was attributed to reduction of oxygen carrying capacity of blood nurturing the tumor. Nitrogen oxides were generated both in burning of tobacco and fossil fuels. The potential dangers of nitrous fumes in industry were reviewed by von Oettingen (4174).

Aliphatic and aromatic compounds. During the 1930's and 1940's, monographs on toxicology were written by McNally (3783) (3902), Lehmann & Flory in German and translated to English by King & Smyth (4304), and Henderson & Haggard (4302). Phenol vapor was tested in animals because of its antiseptic use (4430). The inhalation effects of hydrocyanic acid fumes consisted of pneumonitis in animals (3134). Ingestion and metabolism of polycyclic hydrocarbons were the subject of animal experiments (4327) (4522). Results of animal toxicity studies were applied to patients establishing safety margin of drugs (3972) and worker exposure (4855). The concentrations of aliphatic and aromatic

compounds in cigarette smoke are so low that it would take hundreds of thousands of cigarettes to approach work standards (see Part Four).

Heavy metals in tobacco smoke. During the 1940's, trace levels of arsenic were detected in tobacco and tobacco smoke (4370) (4575). Arsenical insecticides were the origin of the contaminant (3461) (3568). Arsenic in tobacco smoke was suspected as the cause of lung cancer in cigarette smokers (4619) (4950). This suspicion was based on the observation of skin cancer in workers exposed to arsenic (3332) (3550) (4158) (4239) (4570) (4728) (4878). That workers exposed to arsenic developed lung cancer was based on epidemiologic studies (4770) (4839) (4873). Animal studies could not replicate tumors seen in human workers (_____). Cadmium was a known industrial hazard (4714) (4777) but its human carcinogenicity was not accepted until after 1950.

Awareness of literature prior to 1950. Most of the articles under Topic D and Topic E are simply listed without commenting on the validity of their contents. The articles are listed for completeness because most of them were used as citations in references for Part Three, literature review from 1950 to 1966.

E. HOSTAL SUSCEPTIBILITY FACTORS

The monograph entitled *Bronchogenic Carcinoma and Adenoma* by Fried was published in 1948 (a revision of an earlier one published in 1930) and is a **highlight publication.** In the latter edition, Fried concluded that evidence thus far adduced was contrary to the idea that bronchiogenic cancer was caused by tobacco, page 68, **(4801).** On the other hand, Fried accepted the multiplicity of causes attributed to the lung "as an organ that receive dust, bacteria, fumes, gases directly from the air" and "as an organ of convergence of the body ... reached by soluble and particulate matter via the systemic circulation." Fried enumerated factors influencing susceptibility of host such as genetic, diet and nutrition and cellular responsiveness to dust inhalation, infectious disease and trauma. There was an artificial dividing line between dust inhalation covered under Topic E, from occupational/environmental factors under Topic D. For the purpose of this review, chemical vapors, gases, and organic substances, including fossil fuel and combustion emissions are discussed under occupational/environmental factors (Topic D). Occupational hazards consisting of dust particles are discussed under Topic E because of their unique nature in provoking fibrosis and occasionally, lung cancer in susceptible individuals. Inhalations of asbestos and silica are discussed under Topic E because the response is attributed directly to

particulate rather than to a chemical substance or polycyclic aromatic hydrocarbon.

Heredity

Many research contributions on factors determining susceptibility of cancer in mice were derived from inbred strains that were in existence during the 1940's. The following laboratories had strains that either had a high or low incidence of spontaneous tumors and were suitable for investigation of carcinogenic chemicals: National Cancer Institute (4234) (4235), Rockefeller Institute for Medical Research (4058), Jackson Memorial Laboratory at Bar Harbor, ME (4057), National Institute for Medical Research at London (4222), Royal Cancer Hospital at London (4448), University of Leeds (4613), Cornell University Medical College (4121), University of Chicago Medical College (4120), and Yale University Medical School (4474). Strong, from the last mentioned laboratory, attempted to duplicate or imitate in experimental animals the variable genetic background of man. By hybridization of mice and selection toward resistance to methylcholanthrene-induced local tumors, Strong was able to produce selected strains of mice for cancer research (4474). Little, from Jackson Memorial Laboratory, described the incidence of mammary tumor in inbred mice and concluded that the occurrence was dependent not only on genetic constitution but also on physiological variation in the host (4057). Reimann

favored the genetic theory as the cause of cancer and wrote several reviews (4562) (4563) (4959).

Genetic studies in humans have revealed familial aggregation of breast and uterine cancer in pedigree families (4775) (4921). A familial factor had been reported for gastro-intestinal cancer and xeroderma pigmentosa (4448). Twin research revealed genetic susceptibility to tuberculosis (3984). However, it would take two decades later for twin research to support genetic susceptibility to lung cancer. During the 1940's there were several reviews on congenital bronchial adenoma implying that some forms of lung cancer may originate from congenital adenoma (4139) (4232) (4337) (4362) (4514) (4845).

The most significant review on genetic aspects of the cancer problem was prepared by Fritz Blank of New York, under the auspices of the Council of the Bureau of Human Heredity (London) and the Genetics Laboratory, Ohio State University (Columbus, OH). This is a **highlight publication (4418)**. There was a discussion of lung cancer in experimental animals induced by coal tar, but no discussion of human lung cancer. The seven summary statements were as follows:

> "A summary of the present position meanwhile shows that enough evidence has been accumulated to warrant at least the following statements: A. Cancer is not a unit disease, at least so far as its genetic behavior is concerned. Tumors of different sites and types differ in their genetic behavior. B. Therefore it is unlikely that a heritable condition of 'cancer' exists as such. Or, as Haldane has put it: 'The genetics of spontaneous cancer is clearly very complicated, and it is quite ludicrous to ascribe it to the activity of one gene,

> dominant or recessive.' C. There does exist a general inherited disposition, whether of susceptibility or refractoriness, to formation of tumor. By the term 'susceptibility' should be understood the ability of the body to react to specific stimuli with formation of tumor. By the term 'refractoriness' is meant a condition which seems to make the formation of tumors impossible even in the presence of appropriate stimuli. D. In certain persons, factors exist, most probably inherited independently of a general disposition, which govern the localization of the disease. This localization in turn seems to depend on a favorable 'internal environment' in certain tissues or organs. E. If general susceptibility and inherited favorable internal environment are combined in an individual, these factors may be strong enough in themselves to lead to formation of cancer in certain tissues. F. If general susceptibility is great in an individual, even relatively slight irritation by agents of many kinds may lead to formation of cancer. G. But apart from these heritable conditions, there exist purely external cancerogenic agents of various kinds, which are obviously strong enough to lead to formation of cancer in certain tissues, even in persons in whom an inherited predisposition is not distinct or perhaps is too weak to be detected by methods used at present in testing for hereditary traits. Or the predisposition to cancer may not have been inherited but rather acquired under conditions the nature of which is not yet known." page 314, (4418)

Blank's survey of "constitution" as related to cancer will be one of several background papers for the proposed "constitutional hypothesis" prepared after 1950 to explain high incidence of lung cancer in cigarette smokers (See Chapter V).

Diet and Nutrition

Following Hoffman's monograph on *Cancer and Diet* (3701), there was no comprehensive review on the subject during the 1940's. A few authors wrote reviews on carcinogens that included a discussion on influence of diet on susceptibility of

animals to administered carcinogens: Morris, from the National Cancer Institute, reviewed the influence of diet on spontaneous lung tumor formation in mice (4553); Tannenbaum, from Michael Reese Hospital, Chicago, published a series of articles on the effects of feeding, bodyweight on spontaneous and induced skin and hepatic tumors (4093) (4094) (4265) (4475) (4476) (4574) (4970) (4971). Other investigators confirmed the influence of diet and nutrition on tumors in mice induced by benzpyrene (4025) (4918), methylcholanthrene (4662) (4949), and azo compounds (4449) (4452) (4540) (4541) (4769) (4860) (4861). An extrinsic factor in human liver cancer was suspected (4447) but was not identified until two decades later. The following food ingredients have been reported to cause experimental tumors: choline deficiency (4616) (4734) (4924), desoxycholic acid (4415), pyrrol compounds (4435), fat solvents (4525) (4526) (4957), heated cholesterol (4774) (4844) (4930), and tomato juice (3133) (3243). The relevance to human cancer of some of these compounds was not known during the 1940's, other than the structural relationship of cholic acid and pyrrol compounds to methylcholanthrene.

Repeated Bronchopulmonary Irritation

Macklin questioned the importance of chronic respiratory tract irritation relative to constitutional factor and heredity in the etiology of lung cancer (4857). Their

article is selected as a highlight publication:

"As with all other cancers, the problem of the origin of primary cancer of the lung naturally divides itself into two aspects concerned with (1) supposed productive factors acting from outside the body and (2) constitutional factors inherent in the body and varying with the patient and particularly with the 'strain' or line of descent. These agencies are characterized as environmental and hereditary, respectively. The environmental factors may be subdivided into two categories: (a) those that would be encountered in the course of ordinary living, which are the various chronic irritants commonly used to explain human cancer, and (2) those which have been discovered by inducing cancers in animals through the experimental use of specific chemical agents, called carcinogens. As man is not used in the experimental production of cancer, all malignant growths arising in him must come under the heading of (1) tumors induced by the chronic irritations of ordinary life or (2) tumors arising on account of constitution. These may be considered as primary poles, or extremes, useful in our mental processes in the study of the causes of cancer. Actually, the constitutional factor enters into every production of tumor, and the only point which needs to be determined with reference to it is the extent to which it is participating in any given case. So, if the environmental factor is admitted, all tumors are of dual origin. In conclusion, then, we may say that none of the specific diseases or conditions causing chronic inflammation of the lungs can be said to have been proved to be causes of cancer of the lung. They have not been shown to be more common in patients with pulmonary cancer than in a group of the general population of similar age and sex, and until a significant difference can be found between their incidence in those with pulmonary cancer as compared with those without pulmonary cancer their causal relation to this type of cancer will remain purely speculative. This, of course, refers to chronic inflammatory diseases which have antedated the cancer by a sufficient number of years so that they can be excluded from being interpreted as the result, not the cause, of the cancer.

Chronic irritation, especially in the form of chronic inflammatory disease, as a cause of pulmonary cancer has been assumed; the idea has been copied from text to text, repeated from author to author, with little critical analysis of its possible role. Somatic mutations and hereditary factors must be considered and their probable role in causing cancer of the lung

> recognized. True carcinogenic agents for the production of cancer of the lung will no doubt be found as modern industry expands its use of chemicals. But, as some types of cancer will develop in one seventh of men over 40 and since about one fifth of all cancer in males are in the lungs, one thirty-fifth, or about 3 per cent, of all men over 40 will die of this type of cancer. There may be an increase in the incidence of cancer of the lung in any industry beyond the maximal rate for cancer of the lung in the general population, **but one can never state that any patient would not have had cancer of the lung had he not been in that occupation.** Thus even with the presence of carcinogenic agents admitted, their role in causing cancer of the lung cannot be proved in any individual case, nor can they be said to be 100 per cent effective, since a certain percentage of persons exposed to the carcinogenic agents would have had pulmonary carcinoma even without this exposure. The effectiveness of any carcinogenic agent in producing carcinoma of the lung can be judged only by the increment of increase of carcinoma of the lung in large groups, not by its total incidence. It is therefore impossible to assign to any extrinsic factor an absolute role in carcinogenesis in any individual case." pages 926, 954-955, **(4857)**

The above comments were applicable through the 1960's. Even in 1989, it is still "impossible to assign to any extrinsic factor an absolute role in carcinogenesis." It is "impossible" to assign an absolute causative role of cigarette smoking in a lung cancer patient.

Repeated Chemical Irritation. The reaction to repeated inhalation of chemicals, vapors, gases, and substances, consist of cellular death, regeneration metaplasia repair (12112). It has been proposed that repeated exposure of skin to chemical irritants would lead to cancer and this has been supported by repeated skin painting with coal tar or its constituents in mice. However, repeated inhalation of cigarette smoke or chemical vapor and gases have not caused experimental lung cancer (See Topics C

and D above). The following chemicals administered orally or parenterally caused tumors of several organs including the lungs: urethane (4338) (4354) (4757) (4762) (4864) (4925); dinitrotoluene (4426); nitrogen mustards (4817) (4818) (4941); 2-aminofluorene (4843); sulfonamides (4836); and DDT ((4737).

Hueper reported that the intravenous injections of methyl cellulose or polyvinyl alcohol caused pulmonary thesaurosis and atherosclerosis but no neoplasm in rabbits and dogs (3950) (4208) (4238) (4444) (4534) (4537). Prior to 1950, chemical substances administered intravenously could produce lung cancer but it was not known if the cellular mechanism was similar to that elicited by repeated irritation from a chemical inhalant.

Chronic dust diseases of the lung. The association of lung cancer and occupational exposure to dust continued to be reported during the 1940's. The following dust particles were suspected pulmonary carcinogens: asbestos fiber (4090) (42134) (4159) (4228) (4236) (4258) (4268) (4339) (4366) (4439) (4625) (4641) (4650) (4658) (4729) (4824) (4850) (4912) (4927) (4967) (4975); silica (4349) (4358) (4746) (4776) (4837) (4838) (4898) (4967); boiler scaling particles (4433) (4441) (4478) (4517) (4745) (4928); beryllium (4631) (4895); chromate dust (4851) (4852); coal dust (4749) (4958); brick clay for brickworks (4945); diatomaceous earth (4892) (4973); abrasive materials (4779) (4884) (4911); and lead (4036) (4321). These publications were not included in Hueper's monographs that appeared early in the

1940's. The investigation of lung cancer in workers exposed to dust was continued after the 1950's and some of them were tagged as "known carcinogens" by the National Toxicology Program.

Pulmonary tuberculosis and fibrogenic agents. During the 1940's, the differential diagnosis between tuberculosis and lung cancer continued to challenge internist but not as frequently as in earlier decades (4076) (4558) (4913). There was still some suspicion that pulmonary tuberculosis caused tissue reaction that rendered the lung susceptible to chemical or non-chemical carcinogens (4061) (4246) (4961). The basic cellular response consisted of fibrosis which supposedly caused the appearance of cancer in the wall of tuberculous, bronchiectatic and emphysematous cavities (4046) (4360) (4578) (4780). The combination of silicosis and tuberculosis had contributed to the confusion in determining the basic causation of lung cancer (4654) (4791) (4917) (4972).

Physical agents. Radiation continued to be a suspected cause of lung cancer during the 1940's. The specific forms were as follows: radium contained in ores mined at Schneeberg and Joachimsthal (4455); gamma radiation (4645) (4948); ultraviolet radiation (4419) (4420) (4565); and cosmic radiation (4535) (4536) (4934). Additional physical agents have been examined for carcinogenic activity: trauma (4365) (4453) (4479) (4569) (4620) (4630) (4655); and ultrasonic vibration (4830). Henshaw, from the National Cancer Institute wrote a review of physical

carcinogens including mechanical irritation or injury caused by stems of clay pipes in lip epithelioma (4532). The implantation of bakelite discs leading to sarcoma in rats was another example of physical agent causing cancer (4172).

Pulmonary adenomatosis and viruses. Two forms of lung cancer had been suspected as of viral etiology: adenomatosis (4580) (4969), and alveolar cell carcinoma (4066) (4151) (4248) (4368) (4538) (4947). It was believed by some pathologists that both forms originated from the same cell in the lung. In later decades it had not been possible to isolate and transmit any virus from human lung tissue samples although the possibility of viral etiology of lung cancer has not been completely excluded. Techniques that successfully demonstrated papilloma virus in rabbits (4026) (4080) (4167) (4842) and spontaneous tumors in animals (4559) (4581) (4628) (4743) (4834), represented transmission within the same animal species. Isolation of virus from human cancer tissue for transmission to animal species has not been possible. The 1989 nobel laureates in medicine were credited with the discovery of viral induced genetic mutation resulting in cancer.

Environmental and Hostal Interactions

Most information on the subject of interactions between environmental etiologic factors and the susceptible host were derived from experimental animals. During the 1940's and earlier

decades, the need to verify occurrence of interaction in lung cancer patients was implied in review articles on experimental carcinogenesis by the following: Gye (4531); Ivy (4756); Haddow (4629) (4742) (4744); Sannie & Truhaut (3471); and Schabad (2846) (3248) (4571) (4582).

Respiratory tract interactions. The following inhalants have been tested in experimental animals: coal smoke in rabbits (3797); silica and iron oxide in mice (4027); silica and methylcholanthrene (4221); steel grindings in mice (4221); and benzpyrene and several samples of tarred road dust, coal dust, and coal soot in mice (4325). Campbell's conclusions follows:

> "There is a similarity between human lung cancer and mouse lung cancers as regards: (1) agents which increase the incidence of these tumours; (2) the time or age factors; (3) some aspects of the factor of susceptibility; (4) morphology of the tumours. Although the main effect of certain dusts in development of lung cancer appears to be of a prolonged chemical nature, it is not possible at the moment to exclude entirely some effect of prolonged mechanical irritation by the harder or larger collections of dust. A method for comparison of the degree of dust deposit in the various experiments is given for the first time. The increase in incidence of lung tumours in mice by certain dust - tarred road dust with and without the tar, Czechoslovak pitchblende dust, iron oxide, silica, a 'nickel' dust mixture - is statistically significant, although in most cases the average deposits of dust in the lungs are of moderate degree only or less. Care should be taken to reduce exposure to these dusts. Dusts produce a hypertrophy of lymph tissue in the lungs and in the tracheo-bronchial lymph nodes. Some further illustrations of mouse lung cancers and their metastases are given. There is no fundamental reason why the results obtained in mouse experiments with dusts should not be applied to man." page 183, (4325)

In a later issue of the British Medical Journal, Campbell defended his conclusions:

> "After referring to the high incidence of lung cancer in the Schneeberg and St. Joachimsthal miners, attention is drawn in the leading article to the diffrences between the mouse and human lung tumours. It is stated: 'The first and most obvious [difference] is that lung tumours are exceptionally common in some strains of mice; their incidence in control animals in some of these experiments was 20.' I cannot see how this differs from the condition in the above-mentioned miners. Surely, it is a resemblance, not a difference, between the mice and human beings. Further, it is stated that in mice the lung tumours is usually an adenoma in which malignant change is the exception. This was certainly not the case in the experiments with the dusts, where the malignant tumours were more numerous than the simple adenomas. I have not stated that nodular silicosis gives rise to cancer of the lung. My mice did not develop nodular silicosis of the lung during the dusting with silica, although the incidence of lung tumours was definitely increased and there were silicotic nodules in the tracheo-bronchial lymph nodes of about half the mice. In a previous paper I have suggested that when silicosis of the lung - i.e., the nodular condition - develops it may inhibit cancer development. Further, silicosis itself may be consider-ed a type of multiple tumour, although not malignant, of course. In my experiments with iron oxide dust the resulting tumours were more numerous and more malignant than those produced by silica dust. I consider iron oxide at least as active as silica in the case of mice and man. At no time did we find the dusting experiments tedious, since we were the first (1932-4) to obtain positive results. This is due to paying proper atten-tion to the time and other factors. Other researches obtained negative results because their experiments were of too short a duration or they used non-susceptible animals as subjects. The main object of our experiments was to obtain clues to prevention or cure of lung cancer - a difficult problem and not easy to approach." pages 269-270, (4324)

During the 1940's, there were studies on nasal filtration of airborne droplets in rabbits (4720), dust deposition in human tracheobronchial passages (4926), and clearances of carcinogenic

dust particles in workers (3874) (4041) (4322) (4719) (4721) (4738) (4963). The techniques for dust deposition and clearance were not tested for cigarette smoke. Prior to 1950, the only reported airway effect of cigarette smoke was on tracheal cilia of calves (3784).

Airway irritation. The widely accepted theory for pulmonary carcinogenesis prior to 1950 was "irritation" that was widely popularized by Simon's monograph (3702). Several clinicians and pathologists accepted the irritation theory (4129) (4161) (4169) (4253) (4259) (4355) (4768) (4866). Several stages relating to formation of skin cancer were demonstrable in experimental animals (4520) (4543) (4636) (4642) (4653). For pulmonary carcinogenesis, it was not possible to identify in sequence, from initial irritation, pre-neoplastic changes to final cancer in the same group of animals exposed to carcinogens. There were studies on role of respiratory tract on metastasis (4626), and the susceptibility of human lung to second type of cancer after removal of a primary lesion (4479). However, there were no reported observations relating to pre-neoplastic lesions evolving into lung cancer in the same patient.

Biochemistry of cancer. After World War II, the increase in cancer research extended to include biochemistry. There were review articles on the differences between normal and cancerous patients, and the influence of chemically induced cancer in experimental animals (4301) (4423) (4470) (4530) (4579) (4875)

(4880) (4889). There were also reviews on the metabolism of chemical carcinogens, particularly of polynuclear aromatic hydrocarbons (4618) ((4761) (4881) (4976).

Intrinsic carcinogens. During the 1940's, there were reports that extracts from cancerous tissue caused tumors after injection in experimental animals (4459) (4750) (4785) (4786) (4787). The chemical identity of intrinsic carcinogenic factor was not known although hormones were excluded. The growth of some non-pulmonary tumors was influenced by hormones from pituitary (4465) (4664), adrenal cortex (4766) (4940), testis (4627), and ovaries (4438) (4741) (4825). A milk borne tumorigenic agent was detected but not chemically identified in mammary adenoma in mice (4512) (4778). Also in mice, bronchogenic carcinoma was induced from subcutaneous grafts of adult lung tissue impregnated with methylcholanthrene. The tumor incidence was increased if lung grafts were impregnated with stilbestrol in addition to carcinogen. Stilbestrol or other estrogens injected alone did not cause lung carcinoma (4220) (4752). There were early reports of sensitization to tumor cells that prevented successful transplantation directly to lung tissue (4335) (4462) (4463) (4919).

Inadequate scope of cancer research. Although there was a considerable increase in human and financial resources for cancer research after World War II, there were criticisms on the following: First, lack of improvement in treatment of cancer

(4840); Second, need for emphasizing nutritional, cellular and molecular basis for carcinogenesis (4542) (4553) (4577) (4643) (4739) (4764); Third, need to identify responsibility for delay in cancer diagnosis and its correction (4468) (4573) (4763) (4885); and Fourth, selecting human carcinogens among growing list of animal carcinogens (4224) (4429) (4545) (4846) (4923). Most attempts at confirming the carcinogenicity of some chemicals, including constituents of tobacco smoke, and tobacco smoke per se and tobacco tar, gave negative results. The comments of Pfeiffer & Allen from Yale University of School of Medicine, on their attempts to produce cancer in rhesus monkeys with carcinogenic hydrocarbons and estrogens, were applicable to negative results in general:

> "It is evident from the results just described that malignant tumors have not been produced in the monkey by chronic treatment with the female sex hormones and the 3 most commonly used carcinogenic hydrocarbons, methylcholanthrene, benzpyrene and dibenzanthracene. These findings are made more striking by the fact that the carcinogenic compounds have been supplemented in some animals by numerous and extreme inflictions of trauma. Moreover, periodic acute inflammation has been superimposed upon the chronic inflammation that occurs at the sites of application of the carcinogen. This has been especially true when the substance was injected subcutaneously in sesame oil. Negative results are usually considered rather unsatisfactory since their validity is limited in scope. They apply much more rigidly to the experimental conditions than do positive findings. Therefore, a critical analysis of the extent to which the conditions of the present study adhere to the generally accepted requirements for the induction of malignancy is advisable. **Information on all types of experimentally produced tumors indicates that the following factors are of importance: age of host, period of treatment, proper treating agent, method of application, and dosage."** page 106, (4874)

F. SUMMARY STATEMENTS, COUNTER-STATEMENTS AND HIGHLIGHT PUBLICATIONS

The publications explosion during the 1940's is illustrated by citation of over 750 articles that is approximately one-third of the total literature on the subject of pulmonary carcinogenesis. Over 250 articles are quoted above and the remaining 500 are simply referred to by subtopics. However, although articles are briefly mentioned, most are used as secondary citations in articles appearing after 1950 (Part Three), and a few appear after 1966 (Part Four). The publications appearing prior to 1950 will be necessary in the event that a particular form of occupational/environmental or hostal factor will require additional elaboration.

About a score of articles have been selected as highlight publications emphasizing the following conclusions: Prior to 1950, it was not possible to state with absolute certainty that cigarette smoking or any occupational/environmental factor was a significant cause of lung cancer. Several occupational/environmental factors were suspected of causing lung cancer in a susceptible host. Compared to cigarette smoking, the human observations and animal experiments were more extensive in support of the following occupational/environmental factors: fossil fuel products, fuel combustion emissions, and industrial emissions, such as polynuclear aromatic amines,

metalic substances, radioactive substances, and dust particulates. Susceptibility of host to carcinogenic substances were influenced by heredity, diet and nutrition, and tissue reaction to repeated bronchopulmonary irritation. The score of highlight publications support preceding conclusions and supporting details are supplied under Topics A, B, C, D and E.

This concluding Section F consists of a critique of Harris' SOA statements 5.1 to 5.16. The original statements are reproduced below and references used by Harris are numbered using the four-digit citation in the bibliography. Each one of Harris' summary statements is followed by my own counter-statement.

Questionable Increase in Lung Cancer Incidence

> "SOA 5.1. During the period prior to World War I, pathologists, clinicians and vital statisticians began to note an increase in lung cancer - a disease that was relatively obscure prior to 1900. By the late 1920s and 1930s, a dramatic increase in primary lung cancer, predominantly among males, was recognized throughout the United States and Europe. Lung cancer began to overtake cancer of the stomach in clinical and autopsy series and in vital statistics analyses [see Perret (2711); Hoffman (2911) (3131); Arkin and Wagner (3613); Muller 3985); Ochsner and DeBakey 3981) (4164); Menne and Anderson (4156)].

The alleged increase in lung cancer prior to World War I was questionable because of misdiagnosing pulmonary tuberculosis, pulmonary emphysema, parasitic lung disease, and metastatic cancer, for primary lung cancer (see Chapter I). By the late 1920's and 1930's, the increase in primary lung cancer was reported only in cities that has had a thirty year record of autopsies, such as New York, Philadelphia, Boston, Chicago, San

Francisco, Rochester and Detroit. It is wrong to state that the increase in lung cancer incidence "was recognized throughout the United States and Europe" because certification of cause of death was still in its rudimentary stages based on symptomatology with postmortem verification.

> "5.2. At the start, there was controversy concerning the genuineness of the increase in lung cancer incidence. Alternative explanations emphasized improved methods of diagnosis, increased autopsy rates, population aging, changes in disease classification and generally enhanced cancer awareness among physicians. However, such explanations did not accord with other facts, including the increase in the age-specific incidence of lung cancer, the disproportionate rise in lung cancer among males, the rise in lung cancer relative to cancers of other internal organs, and the increased proportion of lung cancers seen at autopsy. Beginning in the late 1920s, a growing number of pathologists, surgeons, vital statisticians, and other scientists realized that, at least since 1920, the rise in lung cancer was genuine, both relatively and absolutely [see Perret (2711); Hoffman (2911) (3131); Mertens (3031); Arkin and Wagner (3613); Muller (3185); Ochsner and DeBakey (3981) (4164); Menne and Anderson (4156); Kennaway and Kennaway (3632) (4759); see also Graham, 1951].

Lung cancer monographers who were also pathologists favored the concept that the increase in lung cancer incidence seen through the 1940's was apparent and unreal. Willis **(4802)**, Fried **(4801)**, Boyd (4130), and Macklin **(4859)** enumerated reasons for misdiagnoses and unreliability of statistics on lung cancer that were applicable prior to, and after 1950.

Cigarette Smoking and Occupational/Environmental Factors

> "5.3 Beginning in the 1920s, a variety of factors were hypothesized as contributing to the striking rise

> in lung cancer. These included: the influenza pandemic of 1918; old tuberculous lesions in lung cancer patients; pre-existing bronchitis and emphysema in lung cancer victims; gasoline fumes containing lead; diesel and gasoline-powered automobile emissions; irritant gases used in World War I warfare; soots, tars and other air pollutants from roads, fuel combustion, and various industrial processes; as well as the rise in cigarette smoking. A concentration of lung cancer cases in the mining district of Schneeberg in Saxony stimulated interest in radioactive substances and certain heavy metals as possible contributors. [See Perret (2711); Hoffman (2911) (3131); Ochsner and DeBakey (4164); Kennaway and Kennaway (3632) (4759)].

Most authorities on lung cancer during the 1940's worked more extensively on non-tobacco causes of lung cancer, than on cigarette smoking. There were human studies and animal experiments supporting the conclusion that lung cancer was caused by the following occupational/environmental factors: fossil fuel products; fuel combustion emissions; soots, tars and air pollutants from roads; industrial emissions; radioactive substances; heavy metals; and polynuclear aromatic hydrocarbons (see above, Topic D).

> "5.4. Beginning in the late 1920s, many surgeons, cancer specialists and other physicians, reporting their clinical experiences with this relatively new cancer, noted that lung cancer patients were almost always heavy cigarette smokers [Table 2]."

Harris selected 21 articles published between 1927 to 1948 to support his statement that "lung cancer patients were almost always heavy cigarette smokers." I have collected more than a hundred additional articles during the three decades prior to 1950, and majority of articles mention cigarette smoke as one of several extrinsic factors in the environment. Approximately a

dozen articles report heavy smoking in their series of lung cancer patients. The remainder of over a hundred articles either quote other investigator's report of heavy smoking or deny that cigarette smoking was a significant causative factor (see Chapter II, page 77; Chapter III pages 204, Chapter IV, page 446).

> "5.5 During the 1930s and early 1940s, the proposition that cigarette smoking caused lung cancer received increasing scientific support (Table 2). Among the several lines of supporting evidence were the following."

For the 1940's, I prepared several tables to illustrate that during this decade, occupational/environmental factors causing lung cancer was receiving increased scientific support. The occupational/environmental human studies and animal experiments exceeded in number the studies that supported the hypothesis that cigarette smoking was a cause of lung cancer (see Topic D, grouping of publications, pages 548 to 561).

<u>Questional Link Between Cancer and Tobacco Use</u>

> "5.6 The concept of cigarette smoking as a cause of lung cancer was consistent with the previously recognized link between pipe or cigar smoking and oral cancer [e.g., Hoffman (3131); Editorial (4117)]."

The link between tobacco use and cancer was explained by direct chemical exposure to cigarette smoke. For oral cancer, link to pipe or cigar smoking was the mechanical irritation of lips (see Supplement, pages 401-410). For lung cancer, cigarette smoking was suspected of causing mucosal irritation, which, together with occupational/environmental factors that also cause

mucosal irritation, lead to lung cancer in a susceptible host.

> "5.7 Further, while pipe and cigar smoking were linked with oral cancer, the widespread inhalation of cigarette smoke, it was reasoned, should be linked mostly to cancer of the lower respiratory tract [e.g., Hoffman (3131); Thys (3540); Ochsner and DeBakey (3981) (4164). Such a hypothesis was supported by observations in cancer patients relating the site of cancer to the type of tobacco used [e.g. Lombard and Doering (2833); Fleckseder (3627); Ahlbom (3765)].

The hypothesis that linked cancer of the lower respiratory tract to type of tobacco used was impossible to prove or disprove because lung cancer patients were also exposed to occupational/ environmental factors, and had undetermined susceptibility associated with heredity, diet and nutrition, and broncho-pulmonary reaction to inhalants. Opinions that strongly linked cigarette smoking to lung cancer were challenged by other investigators who had different interpretations of anti-smoking literature. One anti-smoking physician (Ochsner) reversed his opinion because he could not detect a strong link of heavy smoking in his lung cancer patients.

> "5.8 Moreover, the rise in lung cancer in men parallelled the growth in male cigarette use. The relatively low incidence of lung cancer in women accorded with the delayed emergence of widespread cigarette smoking among females [e.g., Mertens (3031); Lickint (2931); Hoffman (3131); Thys (3540); Arkin and Wagner (3613); Muller (3985); Menne and Anderson (4156); Ochsner and DeBakey (3981) (4164)].

Prior to 1950, most anti-smoking publications emphasized the parallel rise in lung cancer incidence and the prevalence of cigarette use. Some investigators interpreted a lack of increase in lung cancer in women as not supporting a causal hypothesis

(4004) (4079) (4135) 4267) (4554) (4850) (4958). If the hypothesis was correct, incidence in women should have occurred in the 1940's because smoking prevalence had already occurred one or two decades earlier (4772) (4867) (4871).

Animal Experiments on Tobacco Smoke and Coal Tar

> "5.9. In addition, the notion that cigarette smoking caused lung cancer was consistent with the evidence that various tarry products of combustion might be carcinogenic in humans and laboratory animals. Some scientists had produced cancerous lesions in laboratory animals with tobacco smoke and tobacco tars [see Section 4 supra; also Lickint (2931); Muller (3985); Ochsner and DeBakey (4164)]"

Inhalation of tobacco smoke did not induce lung cancer in mice (4914) (4348) and rat (4667). On the other hand, inhalation of coal tar particulate and smoke caused lung cancer in mice. Skin painting with tobacco tar in mice, rats and rabbits, gave conflicting results, whereas squamous cell carcinoma uniformly resulted from skin painting with coal tar and polynuclear aromatic hydrocarbons (4091).

> "5.10 The fact that not all smokers developed lung cancer was consistent with the recognized notion that susceptibility to carcinogens varied among both human populations and experimental strain of animals [e.g., Roffo, as quoted by Grace (4440); American Association of Cancer Research (4348)]."

Susceptibility or sensitivity to lung tumors were demonstrated in selected mice strain receiving polynuclear aromatic hydrocarbons (4086). It should be emphasized that susceptibility or sensitivity was not tested for inhalation of tobacco smoke.

2062855717

There was no experimental support that cigarette smoke could alter susceptibility or sensitivity to known carcinogens.

Pre-existing Lung Disease and Air Pollution

> "5.11. What is more, the evidence in support of alternative explanations was much less impressive. Bronchitis, influenza, and tuberculosis were soon rejected. The growth in lung cancer appeared to precede tarring of the roads. Lung cancer incidence had risen in locations where there had been no increase in coal dust, road tarring or automobile traffic. The predominance of lung cancer among men went against the role of generalized air pollution. Comparisons of lung cancer incidence across occupational categories were inconclusive."

The carcinogenic role of bronchitis, influenza and tuberculosis could not be proven or disproved. During the late 1940's, pulmonary tuberculosis, with its fibrogenic reaction, was still suspected as contributing to appearance of cancer in tuberculous patients. The carcinogenic role of coal dust, road tarring or automobile traffic could not be disproved since animal inhalation experiments consistently showed lung cancer. The higher incidence of lung cancer in cities that were thickly populated and heavily polluted with vehicular and industrial emissions, compared to rural areas and less polluted cities, continued to implicate occupational/environmental factors (4862). That most lung cancer patients in heavily polluted areas were also smokers was raised after 1950 and is described in Part Three.

> "5.12. Finally, although coal dust, radioactive isotopes, chromates, nickel and arsenic compounds and silica remained suspect, exposures to such agents did not appear sufficient to account for the large, dramatic

> increase in lung cancer. As in the earlier experience with oral cancer, researchers recognized that tobacco need not be the only causative factor. [See citations in Ochsner and DeBakey (4164); Menne and Anderson (4156); also Kennaway and Kennaway (4709)]

Any one occupational/environmental factor "need not be the only causative factor." For example, a Schneeberg miner was exposed, not only to radioactive isotope but also to arsenic, silica and cadmium in work environment. He was also exposed to ambient air pollutants such as coal dust, road tar, vehicular emissions and industrial emissions. The same miner might have been a smoker who was ingesting food carcinogens, and had inherited susceptibility to lung cancer. The multiple extrinsic and intrinsic factors influencing susceptibility to lung cancer apply to non-miners, housewives, and outdoor workers listed in a Table of Case Reports (see above, pages 447 to 454).

> "5.13. By the late 1930's, cigarette smoking histories were being intentionally taken among lung cancer patients at major hospitals and centers [see Levin, Goldstein and Gerhardt, 1950; Sadowsky, Gilliam and Cornfield , 1953]."

There was no evidence that by the late 1930's, "cigarette smoking histories were being intentionally taken among lung cancer patients at major cancer hospitals and centers." I have examined publications from cancer hospitals and centers and found that routine questioning of smoking habits occurred only in one Veteran's Hospital. Even publications by clinicians aware of antismoking literature did not report on the smoking habits of

their own series of patients with lung cancer (4046) (4718) (4866).

Control Study From Nazi Germany

> "5.14. By 1939, a carefully age-matched comparison of lung cancer patients with non-cancer patients confirmed a significant excess of heavy smokers in the cancer group and a marked excess of nonsmokers in the control group [Muller (3985)]."

Muller's article appeared just before World War II, when most researchers were highly suspicious of publications written by Nazi physicians. The 1939 article was a summary of Muller's thesis for his doctorate degree. There were no subsequent publications by Muller listed in available literature indices.

> "5.15. During the 1940s, three additional clinical studies comparing lung cancer patients and control subjects [Schairer and Schoniger (4311); Potter and Tully (4560); Wassink (4893) confirmed the previously reported excess of heavy smokers among lung cancer cases (Table 2)]."

Schairer & Schoniger published their article during World War II under the following affiliation: Scientific Institute for Research on the Dangers of Tobacco in Jena, presently in East Germany (4311). There has been no subsequent publication by both authors and one author is listed in a current directory of German physicians. Wassink's publication (4893) related to Dutch patients, who, like German patients, have different prevalence of smoking habits compared to Americans. The claim of Potter & Tully (4560) that there was an excess of heavy smokers among lung cancer cases referred to all forms of tobacco use, mostly pipe

and cigars, and less of cigarette smokers (see Supplement, page 397).

Non-tobacco Factors Causing Lung Cancer

> "5.16. Thus, by late 1930s and early 1940s, a substantial number of researchers had already pointed to cigarette smoking as the main cause of lung cancer (Table 2). Although definitive, unimpeachable evidence was not yet available,the cigarette smoking-lung cancer connection was a sufficiently real possibility to merit serious concern. The notion that cigarette smoking caused lung cancer was well reasoned, clearly articulated, and repeatedly asserted."

The above statements on cigarette smoking equally apply to role of environmental/occupational factors and hostal factors influencing susceptibility. There were more authors who conducted research and published articles, review and monographs on non-tobacco factors causing lung cancer. Quotations from lung monographers conclude this Chapter:

"Neither occupation nor smoking habits seemed of any special significance in this particular series." - Ochsner, DeBakey & Dixon (4773);

"It is quite possible that inhalation of cigarette smoke is an important factor, but proof of this will entail much more pathological and experimental research." - Willis (4802);

"Evidence thus far adduced is contrary to the idea that bronchogenic cancer is caused by tobacco." - Fried (4801).

2062855721